

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A method of treating a subject with cancer by administration of a macrocyclic metal chelate, said method comprising the steps of:

(a) administering to said subject an antibody comprising an antigen recognition domain that recognizes said macrocyclic metal chelate, wherein said antibody comprises:

a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain and

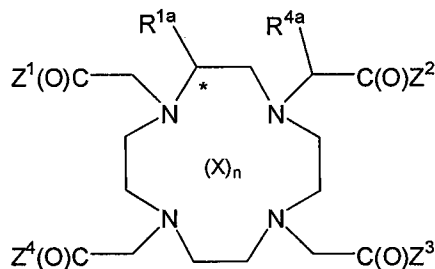
a targeting moiety that binds specifically to a cancer cell by binding with a member selected from a cell surface receptor and cell surface antigen, thereby forming a cell-antibody complex;

wherein said macrocyclic metal chelate is substituted or unsubstituted 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), and comprises a reactive functional group with a reactivity complementary to said antibody reactive site; and

(b) administering to said subject said macrocyclic metal chelate, thereby forming a covalent bond between said reactive site and said reactive functional group.

2. – 5. (Canceled).

6. (Currently amended) The method of claim 1, wherein said substituted or unsubstituted macrocyclic metal chelate comprises 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) and has the formula:



wherein

R^{1a} and R^{4a} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and linker moieties;

X is a member selected from a lanthanide ion, an actinide ion, an alkaline earth metal ion, and a group IIIb transition metal ion;

Z^1 , Z^2 , Z^3 and Z^4 are members independently selected from OR^1 and NR^1R^2

in which

R^1 and R^2 are members independently selected from H, substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl;

n is a member selected from 0 and 1.

7. (Cancelled).

8. (Previously presented) The method of claim 6, wherein the carbon atom marked * is of S configuration.

9. (Cancelled)

10. (Previously presented) The method of claim 1, wherein said targeting moiety binds specifically to said cell surface antigen.

11. (Original) The method of claim 1, wherein the targeting moiety is covalently attached to said antibody.

12. (Previously presented) The method of claim 10, wherein the targeting moiety is a second antibody.

13. (Original) The method of claim 11, wherein the targeting moiety specifically binds to a protein on a cancer cell.

1 14. (Original) The method of claim 1, wherein the subject is a mammal.

1 15. (Previously presented) The method of claim 14, wherein the mammal is a human.

1 16. (Withdrawn) A method of *in vivo* imaging, said method comprising the steps of:

(a) administering to a subject an antibody comprising an antigen recognition domain that recognizes a macrocyclic metal chelate, wherein said antibody comprises a recognition moiety that binds specifically to a cell, thereby forming a cell-antibody complex;

(c) administering to said subject said metal chelate, thereby specifically binding said compound to said antibody to form a cell-antibody-metal chelate complex; and

(d) detecting said cell-antibody-metal chelate complex.

1 17. (Withdrawn) The method of claim 16, wherein said metal chelate comprises four nitrogen atoms.

1 **18.** (Withdrawn) The method of claim 16, wherein the step of detecting is by positron emission
2 tomography.

1 **19.** (Withdrawn) The method of claim 16, wherein the step of detecting is by magnetic +resonance
2 imaging.

1 **20.** (Withdrawn) The method of claim 16, wherein the step of detecting is by detection of lanthanide
2 luminescence.

1 **21.** (Withdrawn) The method of claim 16, further comprising, between steps (a) and (b),
2 administering a clearing agent to said subject.

1 22. (Withdrawn) The method of claim 16, wherein the subject is a mammal.

1 **23.** (Withdrawn) The method of claim **22**, wherein the mammal is a human.

1 24. (Previously presented) The method according to claim 1 wherein said antibody has the structure:

2 (Ab)_n-L-T

3 wherein,

4 n' is an integer selected from 1 to 10 ;

5 Ab represents said antibody;

6 L is a member selected from a chemical bond and a linking group that may contain one or
7 more functional groups; and

8 T is said targeting moiety.

1 25. (Canceled).

1 26. (Previously presented) The method of claim 24, wherein said targeting moiety is a second
2 antibody that binds specifically to a cell surface antigen.

1 27. (Previously presented) The method according to claim 24 wherein said antibody is administered
2 to said subject as a pharmaceutical composition comprising said antibody and a pharmaceutically
3 acceptable carrier.

1 28. (Canceled)

1 29. (Cancelled).

1 30. (Previously presented) The method according to claim 1, wherein said cell is a cancer /*-cell.

1 31 (Canceled)

2 32. (Cancelled).

1 33. (Previously presented) The method according to claim 6, wherein

2 R^{1a} and R^{4a} are H;

3 Z¹, Z², Z³ and Z⁴ are OH;

4 and n is 1.

1 34. (Previously presented) The method according to claim 33, wherein said targeting moiety is a
2 second antibody that binds specifically to a cell surface antigen.

1 35. (Previously presented) The method according to claim 34, wherein said targeting moiety is anti-
2 CEA.

1 36. (Previously presented) The method according to claim 33, wherein said targeting moiety is anti-
2 CEA.

1 37. (Currently amended) The method according to claim 1, wherein said antigen recognition domain
2 of said antibody has a first sequence having at least 95 % sequence identity with SEQ ID NO.1, and
3 comprises CDR1 having the amino acid sequence of SEQ ID NO:2 and CDR3 having the sequence of
4 SEQ ID NO:4; and wherein said antibody has a second sequence having at least 95 % sequence identity

with SEQ ID NO. 5, and comprises CDR1 having the amino acid sequence of SEQ ID NO:6 and CDR3 having the sequence of SEQ ID NO:8.

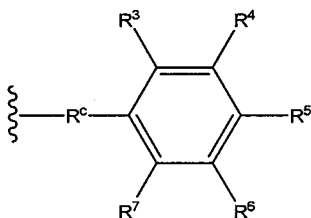
38. (Previously presented) The method according to claim 1, wherein said reactive site comprises sulfur.

39. (Cancelled) The method according to claim 1, wherein said antibody is purified.

40. (Previously presented) The method according to claim 6, wherein R^{1a} is a member independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and linker moieties.

41. (Previously presented) The method according to claim 6, wherein R^{4a} is a member independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and linker moieties.

42. (Previously presented) The method according to claim 6, wherein said DOTA further comprises an arylalkyl moiety having a structure according to the formula:



wherein

R^c is an unsubstituted unbranched alkyl linker;

R^3 , R^4 , R^5 , R^6 and R^7 are members independently selected from H, halogen, NO_2 , CN, X^1R^8 , NR^9R^{10} , and $C(X^2)R^{11}$,

wherein

X^1 is a member selected from O, NH, and S;

X^2 is a member selected from O, S, and NH;

R^8 and R^9 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyl and $C(Z^3)R^{12}$

wherein

Z^3 is a member selected from O, S and NH;

16 R^{12} is a member selected from substituted or unsubstituted alkyl, substituted or
17 unsubstituted heteroalkyl and OR^{13}
18 wherein
19 R^{13} is a member selected from substituted or unsubstituted alkyl,
20 substituted or unsubstituted heteroalkyl, substituted or
21 unsubstituted aryl, and substituted or unsubstituted heteroaryl;
22 R^{10} is a member selected from H, substituted or unsubstituted alkyl, substituted or
23 unsubstituted heteroalkyl, and OH, and
24 R^9 and R^{10} taken together are optionally ($=C=S$);
25 R^{11} is a member selected from H, halogen, substituted or unsubstituted alkyl, substituted
26 or unsubstituted heteroalkyl, OR^{14} , and $NR^{15}R^{16}$,
27 wherein
28 R^{14} is a member selected from H, substituted or unsubstituted alkyl, substituted
29 or unsubstituted heteroalkyl, and $C(O)R^{17}$,
30 wherein
31 R^{17} is a member selected from substituted or unsubstituted alkyl, and
32 substituted or unsubstituted heteroalkyl; and
33 R^{15} and R^{16} are members independently selected from H, substituted or
34 unsubstituted alkyl, and substituted or unsubstituted heteroalkyl.

1 43. (New) The method according to claim 1, wherein said antigen recognition domain of said
2 antibody comprises:

3 i) a light chain comprising:

4 a) a first CDR having the sequence of SEQ ID NO:2;

5 b) a second CDR having a sequence selected from the group consisting of:

6 i) SEQ ID NO:3; and

7 ii) SEQ ID NO:3 containing a cysteine substitution wherein position 2 is
8 substituted by a cysteine;

9 c) a third CDR having the sequence of SEQ ID NO:4;

10 ii) a heavy chain comprising:

11 a) a first CDR having the sequence of SEQ ID NO:6;

12 b) a second cDR having a sequence selected from the group consisting of:

13 i) SEQ ID NO:7;

14 ii) SEQ ID NO: 7 containing a cysteine substitution wherein position 5 has been
15 substituted by a cysteine;

16 iii) SEQ ID NO:7 containing a cysteine substitution wherein position 6 has been
17 substituted by a cysteine; and

18 iv) SEQ ID NO:7 containing a cysteine substitution wherein position 7 has been
19 substituted by a cysteine;

20 c) a third CDR having the sequence of SEQ ID NO:8;

21 wherein said antibody comprises at least one of said cysteine substitutions, and wherein said antibody
22 binds substituted or unsubstituted 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA).